REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Objections to the specification

The specification was objected to based on the allegation that "it contains references to the tables that are presented as separate entities" (Office Action, May 20, 2003; page 2).

As requested by the Examiner, Tables 1 through 7 have been amended such that they precede the claims. The pages containing the tables are being renumbered solely to satisfy the Examiner's request. Applicants maintain that the guidelines set out previously (on pages 4-5 of the Office Action of November 19, 2002) are the **preferred** layout for patent applications, and are not an absolute requirement.

For at least these reasons, withdrawal of this objection is requested.

The specification was objected to based on the allegation that "it contains an embedded hyperlink and/or other form of browser-executable code" (Office Action, May 20, 2003; page 2).

In the present amendment, the text string "http://www." has been removed from the web addresses found in the specification. The web addresses by themselves, lacking the text string "http://www.", are not considered to be browser-executable code (see, e.g., M.P.E.P. § 608.01).

For at least these reasons, withdrawal of this objection is requested.

The specification was objected to based on the allegation that it "refers to 'GenBank ID g181382' . . . where it appears 'GenBank ID 181382' is intended" (Office Action, May 20, 2003; page 3).

A skilled artisan would understand that GenBank identifiers may be either a numeral or a combination of the numeral preceded by the lower case letter "g." Historically, both of these types of GenBank identifiers have been used throughout the literature, and one of skill in the art would

reasonably understand the meaning of these identifiers. Therefore, the use of "g181382" as a GenBank identifier is appropriate.

Nevertheless, to expedite prosecution, the specification has been amended to recite "GenBank ID 181382" instead of "GenBank ID g181382." Applicants do not concede to the Patent Office position; Applicants are amending the specification solely to obtain expeditious allowance of the instant application. Therefore, withdrawal of this objection is requested.

II. Utility rejection under 35 U.S.C. § 101

The rejection of claims 3-7, 9, 11, and 46-53 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in human liver tumor tissue (Specification, e.g., at page 23, lines 5-8; and Tables 5 and 6). The claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the cytochrome P450 family, whose biological functions include the oxidative metabolism of substrates such as natural compounds, drugs, carcinogens, mutagens, and xenobiotics (e.g., at page 1, lines 11-25). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this response the declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Office Action with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their

activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as highly specific probes in a cDNA microarray:

> Persons skilled in the art would [on July 14, 2000] appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15)

The Office Action does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Office Action contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological functions, or the biological functions of their encoded polypeptide. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the protein encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise biological functions.

The Office Action asserts that "the specification does not provide any evidence of an enzymatic activity for the protein encoded by SEQ ID NO:2. Therefore, as disclosed, a protein of SEQ ID NO:1 is an uncharacterized protein. In view of this, an isolated protein of SEQ ID NO:1 has no specific, substantial or well-established utility" (Office Action, May 20, 2003; page 4). By these statements, it appears that the Office Action would require an actual reduction to practice of the claimed invention in order to satisfy the utility requirement of 35 U.S.C. § 101. However, an actual reduction to practice is not necessary. The polynucleotide sequence of SEQ ID NO:2 and the amino acid sequence of its encoded polypeptide, SEQ ID NO:1, have been explicitly disclosed in the specification, thus satisfying the statutory requirements by a constructive reduction to practice. In conjunction with the disclosure in the specification and the knowledge in the art at the time the application was filed, the constructive

reduction to practice of the claimed polynucleotides more than adequately sets out a patentable utility for the claimed invention.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Office Action. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotides.

The instant application claims the benefit of a United States provisional patent application (Lal et al.; U.S. Ser. No.60/218,934, filed July 14, 2000; hereinafter "the Lal '934 application"). The instant application and the Lal '934 application were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the instant application and the Lal '934 application.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Lal '934 application on July 14, 2000 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as highly specific probes for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration at, e.g., ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that "the specification of the Lal '934 application would have led a person skilled in the art on July 14, 2000, who was using gene expression

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '934 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

monitoring in connection with developing new drugs for the treatment of cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [on July 14, 2000] appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-July 14, 2000 publications showing the state of the art on July 14, 2000 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include over three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on July 14, 2000 (and for several years prior to July 14, 2000) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Lal '934 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '934 application at the time it was filed "would have wanted their cDNA microarray to have a probe to a SEQ ID NO:1-encoding polynucleotide because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to July 14, 2000" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than

sufficient reason to compel the conclusion that the Lal '934 application disclosed to persons skilled in the art at the time of its filing substantial, specific, and credible real-world utilities for the claimed polynucleotides.

Nowhere does the Office Action address the fact that, as described, for example, on pages 51-53 and 62-65 of the Lal '934 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed SEQ ID NO:2 polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); M.P.E.P. § 2107.01 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., **they are useful in analyzing compounds**)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in liver tumor cells (see the Lal '934 application at, e.g., page 23, lines 3-6; and Tables 5 and 6), and expresses a protein that is a member of a class known to play a role in the oxidative metabolism of substrates such as natural compounds, drugs, carcinogens, mutagens, and xenobiotics, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use.

In other words, the person of ordinary skill in the art can derive more information about a potential drug candidate for cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, or potential toxin, with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-July 14, 2000 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '934 application was filed (Bedilion Declaration ¶¶ 10-14; and Tabs A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Declaration at Tab D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58; and col. 18, lines 25-30).

Literature reviews published before the filing of the Lal '934 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

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> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a **pattern** of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. [emphasis added]

Rockett et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems and potential, Xenobiotica, 1999, 29:655-691.

In another pre-July 14, 2000 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. **The amplicons can also be used directly by, for example, arraying onto glass for expression analysis**, for DNA binding assays, or for any direct DNA assay. [emphasis added]

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proceedings of the National Academy of Sciences USA, 1997, 94:8945-8947.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety

assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis, 1999, 24:153-159; Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology – potentials and limitations, Toxicology Letters, 2000, 112-113:467-471.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environmental Health Perspectives, 1999, 107:681-685. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological

compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

C. The uncontested fact that the claimed polynucleotides encode a polypeptide in the cytochrome P450 family also demonstrates utility

In addition to having substantial, specific, and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotides encode a polypeptide having the sequence shown as SEQ ID NO:1 in the patent application and referred to as CYTPV in that application. Applicants have demonstrated that CYTPV is a member of the cytochrome P450 family, and that the cytochrome P450 family includes proteins which are involved in the oxidative metabolism of substrates such as natural compounds, drugs, carcinogens, mutagens, and xenobiotics.

The Patent Office does not dispute any of the facts set forth in the previous paragraph. Neither does the Patent Office dispute that, if a polynucleotide encodes a polypeptide that has a substantial, specific, and credible utility, then it follows that the polynucleotide also has a substantial, specific, and credible utility.

The Patent Office must accept the Applicants' demonstration that the polypeptide encoded by the claimed polynucleotides is a member of the cytochrome P450 family and that utility is proven by a reasonable probability unless it can be demonstrated through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Patent Office has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Patent Office provided any evidence that any member of the cytochrome P450 family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the polypeptide encoded by the claimed polynucleotides must, like the other members of the cytochrome P450 family, be useful.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence the Patent Office may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or

entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotides and the encoded polypeptide, and millions of other sequences, throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the claimed polynucleotides, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed SEQ ID NO:2 polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Office Action's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Office Action attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not "specific and substantial asserted" utilities (Office Action, May 20, 2003; page 3). The Office Action is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Office Action's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Office Action, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Office Action would require, in addition, that the Applicants provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Office Action would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, e.g., ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility

because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Office Action has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Office should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotides encode a polypeptide in the cytochrome P450 family, the Office Action refused to impute the utility of the members of the cytochrome P450 family to CYTPV. The Office Action of May 20, 2003 takes the position that, unless Applicants can identify which particular biological function within the class of cytochrome P450 proteins is possessed by CYTPV (e.g., which particular substrates are metabolized by CYTPV), utility cannot be imputed (Office Action, May 20, 2003; pages 3-4). To demonstrate utility by membership in the class of cytochrome P450 proteins, the Office Action would require that all cytochrome P450 proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Office Action addresses CYTPV as if the general class in which it is included is not the cytochrome P450 family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the cytochrome P450 family does not. The cytochrome P450 family is sufficiently specific to rule out any reasonable possibility that CYTPV would not also be useful like the other members of the family.

Because the Office Action has not presented any evidence that the class of cytochrome P450 proteins has any, let alone a substantial number, of useless members, the Office Action must conclude that there is a "substantial likelihood" that the CYTPV encoded by the claimed polynucleotides is useful. It follows that the SEQ ID NO:2 polynucleotide also is useful.

Even if the Office Action's "common utility" criterion were correct – and it is not – the cytochrome P450 family would meet it. It is undisputed that known members of the cytochrome P450 family are proteins involved in the oxidative metabolism of substrates such as natural compounds, drugs, carcinogens, mutagens, and xenobiotics. A person of ordinary skill in the art need not know any more about how the claimed invention participates in the oxidative metabolism of substrates such as natural compounds, drugs, carcinogens, mutagens, and xenobiotics to use it, and the Office Action presents no evidence to the contrary. Instead, the Office Action makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given cytochrome P450 carries out the oxidative metabolism of any particular substrate. The Office Action then goes on to assume that the only use for CYTPV absent knowledge as to how the cytochrome P450 actually works is further study of CYTPV itself.

Not so. As demonstrated by Applicants, knowledge that CYTPV is a cytochrome P450 is more than sufficient to make it useful for the diagnosis and treatment of cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders. Indeed, CYTPV has been shown to be expressed in human liver tumor tissues. The Patent Office must accept these facts to be true unless the Patent Office can provide evidence or sound scientific reasoning to the contrary. But the Patent Office has not done so.

C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Office Action's rejection of the claims at issue is tantamount to a rejection on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Office Action's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107.01):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the Patent Office's Training Materials to be useful, as are polynucleotide sequences used, for example, as markers.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases

state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete (Bedilion Declaration at ¶ 15).

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polynucleotide is dependent on the **identity** of that polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. **No two human-expressed polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

As an example, any histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes**. A drug candidate which alters expression of a histone gene is toxic because disruption of

such a pervasively-expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of a histone gene is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene in toxicology testing is specific and substantial because a toxicology test using that histone gene cannot be replaced by a toxicology test using a different gene, including any other histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., at pages 49-50), chromosomal mapping (e.g., at pages 54-55), etc.

IV. By Requiring the Applicants to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Office Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was

determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B (*Montedison,* 664 F.2d at 374-375).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

III. Utility/enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 11, and 46-53 were rejected under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility under 35 U.S.C. § 101.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

IV. Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 11 and 49-50 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action asserts that "[n]aturally occurring nucleotide sequences having at least 95% identity to SEQ ID NO:2 encode variants the function of which **may or may not be altered**. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the

structure of any naturally occurring alleles" (Office Action, May 20, 2003; page 5; emphasis in original). This rejection is traversed.

Nowhere in the Office Action does the Patent Office offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Applicants were in possession of the claimed polynucleotide variants. The Office Action instead states that "[t]he general knowledge in the art concerning alleles dose [sic] not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others" (Office Action, May 20, 2003; pages 5-6).

The Office Action's position is contrary to the Patent and Trademark Office's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** [footnotes omitted; emphasis added]

Here, there simply is no requirement that the claims recite the functions of particular variants because the claims already provide sufficient structural definition of the claimed subject matter. That is, the claimed variants are defined in terms of SEQ ID NO:2. Because the claimed variants are defined in terms of SEQ ID NO:2, the precise chemical structure of every variant within the scope of the claims can be discerned. Furthermore, there is no requirement that the claims explicitly recite the sequence of every variant within the scope of the claims. The Office Action's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention.

V. Enablement rejections of "fragments" under 35 U.S.C. § 112, first paragraph

Claims 51-53 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed fragments. In particular, the Office Action asserts that "the specification, while being enabling for a DNA encoding SEQ ID NO:1 and fragments **consisting** of 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof, does not reasonably provide enablement for a DNA **comprising** 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof" (Office Action, May 20, 2003; page 6; emphasis added). Such, however, is not the case.

The Office Action's assertions seem to imply that the use of the transitional phrase "comprising" in claims 51-53 requires that the specification provide enablement for any possible element which could be a part of, but is not essential to, the claimed subject matter. However, the transitional phrase " '[c]omprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." M.P.E.P. § 2111.03 (citing *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997)).

The specification has provided enablement for polynucleotides comprising fragments of SEQ ID NO:2. For example, the specification discloses that oligomers which "contain a fragment of a polynucleotide encoding CYTPV" (i.e., a polynucleotide "comprising" a fragment of a polynucleotide encoding CYTPV) can be used in diagnostic assays (Specification, e.g., at page 50, lines 12-18). In another example, the specification discloses that an oligonucleotide can be labeled, thus creating a hybridization probe which is essentially a polynucleotide "comprising" the oligonucleotide (e.g., at page 47, line 33 to page 48, line 4; and page 63, line 31 to page 64, line 7). One of skill in the art would understand how to make and use polynucleotides "comprising" the recited fragments of SEQ ID NO:2, without an explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides comprising fragments of SEQ ID NO:2. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides comprising fragments of SEQ ID NO:2.

For at least the above reasons, withdrawal of this rejection is requested.

VI. Rejections under 35 U.S.C. § 112, second paragraph

Claims 3, 9, 11, and 48-50 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of "% identity" in the claims is indefinite. The Office Action asserts that "in view of the prior art that has homology that is very close to the claimed homology," "[i]t is impossible to make an accurate comparison of the two highly homologous sequences without knowing the program and the algorithms and the parameters that are used" (Office Action, May 20, 2003; page 9). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other

words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

The Office Action is incorrect in requiring a disclosure of the program, algorithms, and parameters that are used to determine the % identity between two sequences in order for there to be an "accurate comparison" between the sequences. All that is necessary is that one of skill in the art be able to reasonably determine what is within the scope of the claim. In the present case, one of skill in the art would reasonably understand whether any particular sequence was, for example, "at least 95% identical to" a reference sequence, without needing a disclosure of any particular program, algorithms, and/or parameters. This is because a skilled artisan would know which programs, algorithms, and parameters could be reasonably used to determine the % identity between two sequences.

As an example, the Office Action states that "Jaiswal et al. (GenBank accession Z00036, . . .) teach a DNA encoding human cytochrome P3(450) that is 93.6% (best local similarity of 97.5%) identical to SEQ ID NO:2" (Office Action, May 20, 2003; page 10), in relation to the rejection under 35 U.S.C. § 102 (addressed below). The Examiner, being a skilled artisan, was able to reasonably determine the % identity between the polynucleotide of Jaiswal et al. and the SEQ ID NO:2 polynucleotide, despite the alleged lack of disclosure of the programs, algorithms, and parameters to be used in such a determination. This is compelling evidence that the claims meet the requirements of 35 U.S.C. § 112, second paragraph.

Furthermore, the Office Action is wrong in asserting that the program, algorithms, and parameters used to determine the % identity between two sequences are not known. The specification provides examples of programs, algorithms, and parameters that would allow a skilled artisan to reasonably determine the % identity between two sequences. For example, the specification discloses that "[p]ercent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. . . For pairwise alignments of polynucleotide sequences, the default

parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and 'diagonals saved'=4. The 'weighted' residue weight table is selected as the default" (Specification at page 13, lines 13-21). Similarly, the specification discloses programs, algorithms, and parameters for determining % identity between two polypeptides (e.g., at page 14, lines 25-31). Thus, the recitation of % identity in the claims meets the requirements of 35 U.S.C. § 112, second paragraph, at least because the specification discloses programs, algorithms, and parameters for reasonably determining % identity between two sequences.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VII. Rejections under 35 U.S.C. § 102(b)

Claims 11, 49, and 50 were rejected under 35 U.S.C. § 102(b) because the recited polynucleotides are allegedly anticipated by Jaiswal et al. (GenBank Accession Z00036; September 12, 1993). The Office Action asserts that Jaiswal et al. "teach a DNA encoding human cytochrome P3(450) that is 93.6% (best local similarity of 97.5%) identical to SEQ ID NO:2, a vector containing it and a cell expressing thereof. The rejection is made in view of the indefiniteness of the claims, *supra*" (Office Action, May 20, 2003; page 10). This rejection is traversed.

As discussed above in § VI, the claims are not indefinite because one of skill in the art would reasonably understand how to determine the % identity between two sequences. The Examiner, being a skilled artisan, was able to reasonably determine the % identity between the polynucleotide of Jaiswal et al. and the SEQ ID NO:2 polynucleotide, despite the alleged lack of disclosure of the programs, algorithms, and parameters to be used in such a determination. Thus, the alleged indefiniteness of the claims does not support a *prima facie* case that the claims are anticipated by Jaiswal et al.

Moreover, the Office Action asserts that the DNA of Jaiswal et al., which is 93.6% identical to SEQ ID NO:2, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has not shown

how Jaiswal et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection is requested.

The polynucleotide variants recited by claims 11, 49, and 50 are not taught by Jaiswal et al. Claims 11 and 49 recite polynucleotide variants at least **95%** identical to SEQ ID NO:2, and claim 50 recites polynucleotide variants at least **98%** identical to SEQ ID NO:2. Jaiswal et al. do **not** teach polynucleotides at least 95% identical to SEQ ID NO:2, or polynucleotides at least 98% identical to SEQ ID NO:2. Therefore, Jaiswal et al. do not anticipate the polynucleotide variants of claims 11, 49 and 50, and withdrawal of this rejection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: August 19, 2003

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